Comparison of Long and Short GnRH-a/hMG Ovarian Stimulation Protocols in Assisted Reproduction

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Abstract :

Objective: *To evaluate the outcome of long and short GnRH-a/hMG ovarian stimulation protocols in assisted reproduction.*
Design: *A retrospective review.*
Setting: *The study was conducted in a University Hospital in Northern Thailand.*
Patients: *A group of 141 consecutive patients who underwent 186 cycles of ovulation induction for assisted conception at the Infertility Clinic, Maharaj Nakorn Chiang Mai University Hospital, from January 1990 to August 1992.*
Main outcome measures : *Cycle cancellation rates, amount of hMG used, duration of treatment, estradiol levels on the day of hCG injection, number of oocytes retrieved, fertilization rates, preclinical and clinical pregnancy rates, abortion rates and incidence of ovarian hyperstimulation syndrome (OHSS).*
Results: *The long protocol required significantly more hMG, longer duration of treatment, had a higher incidence of OHSS, higher fertilization and abortion rates. No statistically significant differences in cycle cancellation rates, numbers of oocytes retrieved and pregnancy rates were found.*
Conclusion: *Short protocol may be more preferable than long protocol in terms of patients' expense, convenience and side-effects. (Thai J Obstet Gynaecol 1993; 5: 91-98.)*

Key words : assisted reproduction, long and short ovarian stimulation protocols

Natural cycle in vitro fertilization (IVF) has now largely been abandoned in favour of ovarian stimulation cycles for assisted conception because the chance of pregnancy is principally determined by the number of oocytes or embryos replaced[1-3]. In stimulated cycles premature luteinizing hormone (LH) surge, with its deleterious effects on follicular, luteal endocrinology or on uterine environment, accounts for a 10-30% cancel-

lation in IVF cycles[4-6]. To overcome this problem gonadotropin releasing hormone agonist (GnRH-a) has been introduced as the adjuvant controlling ovarian stimulation to reduce the endogenous secretion of LH[6,7]. The use of such agonists has been shown to significantly reduce cancellation rate and to efficiently increase the number of oocytes and embryos when compared with cycles stimulated with clomiphene citrate-human menopausal gonadotropins (CC-hMG) or hMG alone[7-9]. Different protocols for timing GnRH-a have been described[3, 6-10]. In practical terms, these can be reduced to two principle categories: a long (suppression) or a short (flare up) protocols. There is still some controversy regarding which protocol is better than the other in terms of oocyte recovery rates, number and quality of embryos available for transfer, and pregnancy rates.

In the present study, we compared the long and short GnRH-a/hMG ovarian stimulation protocols for assisted reproduction in our infertile patients.

Materials and Methods

The study included 141 consecutive patients who underwent 186 cycles of ovulation induction for assisted conception at the Infertility Clinic, Maharaj Nakorn Chiang Mai University Hospital from January 1990 to August 1992. All patients received complete basic infertility investigations and had failed conventional therapy for their infertility problems before they were considered for assisted reproduction. The details of our program have been described previously[11-13].

In brief, patients were allocated to either the long or short GnRH-a ovarian stimulation protocols at the discretion of their attending physicians. Buserelin acetate (Suprefact®, Hoechst) was administered intranasally at a dose of 100 ug 6 times per day, starting in the midluteal of the preceding cycle in the long protocol, or on the first day of the current cycle in the short protocol. In both regimens, hMG (Pergonal®, Serono) and/or follicle stimulating hormone (FSH, Metrodin®, Serono) were given intramuscularly according to the patients' age and previous responses, from cycle day 3 onward. Pelvic sonogram was done on the first day of the cycle as baseline, and then on a daily basis from day 8 of the cycle to monitor follicular growth. Daily measurement of serum estradiol by specific radioimmunoassay (Estradiol Maia Kit, Biodata Products) was done from day 6 of the cycle. Human chorionic gonadotropin (hCG, Profasi®, Serono) 5000-10000 IU was given intramuscularly when ultrasound demonstrated 2 or more ovarian follicles exceeding 17 mm in diameter and the estradiol level reached ≥ 300 pg/ml per dominant follicle. Buserelin was stopped on the day of hCG injection and oocyte retrieval was scheduled 34-36 hours later, followed by gamete intrafallopian transfer (GIFT), zygote intrafallopian transfer (ZIFT) or in

vitro fertilization and embryo transter (IVF & ET). Luteal phase was supported with hCG 1500 IU intramuscularly on days 2, 5, 8, and 11 dating from oocyte recovery.

Criteria for cycle cancellation included an insufficient ovarian response (poor estradiol increase), a decrease in estradiol level (falling levels ≥ 20% of previous levels before fulfilment of criteria for hCG administration), and excessive ovarian response.

Statistical analyses were performed using Student's t-test, Fisher exact test and Chi-square test when appropriate. The results were considered significant at value $p < 0.05$.

Results

Fifteen ovarian stimulation cycles out of 186 were cancelled before oocyte retrieval (Table 1), leaving 171 cycles for analysis. Of these, 87 were assigned to short and 84 to long protocols. The mean ages of the patients, duration and aetiologies of infertility, as well as types of assisted reproduction were comparable in the two groups (Table 2).

Table 1 Reasons for cycle cancellation before oocyte retrieval

Causes	Short protocol	Long protocol
Insufficient ovarian response	4	8
Excessive ovarian response	-	1
Falling E2 levels	1	1
Total cancellation*	5/92	10/94

* p = 0.2817, no significant difference by Fisher exact test.

Table 2 Patients profiles

	Short protocol (n=87)	Long protocol (n=84)	p value
Mean ages (years)[a]	35.6 ± 7.9	34.9 ± 3.3	NS[b]
Duration of infertility (years)	7.1 ± 4.2	7.0 ± 3.9	NS
Aetiologies of infertility[c]			
Tubal obstruction[d]	37 (42.5%)	45 (53.6%)	NS
Endometriosis[d]	24 (27.6%)	17 (20.2%)	NS
Male factor[d]	23 (26.4%)	18 (21.4%)	NS
Unexplained[e]	9 (10.3%)	7 (8.3%)	NS
Type of assisted reproduction			
IVF & ET[d]	47 (54.0%)	55 (65.5%)	NS
GIFT[d]	27 (31.0%)	21 (25.0%)	NS
ZIFT[e]	3 (3.4%)	1 (1.2%)	NS
GIFT + IVF & ET[e]	10 (11.5%)	7 (8.3%)	NS

a=Unpaired t-test
b=NS, nonsignificant
c=Some patients had more than one infertility factors
d=Chi-square test
e=Fisher exact test

Table 3 Comparison of short and long GnRH-a superovulation protocols

	Short protocol (n=87)	Long protocol (n=84)	p value
Numbers of hMG ampoules	21.2 ± 9.2	30.1 ± 13.4	0.0030
Days of GnRH-a/hMG treatment	11.3 ± 2.1	19.8 ± 3.6	<0.000001
E2 level on the day of hCG injection (pg/ml)	1791.5 ± 801.4	2007.9 ± 883.9	NS[a]
Numbers of oocytes retrieved	7.1 ± 4.8	8.8 ± 5.2	NS
Fertilization rates (%)	226/447 (50.6%)	301/496 (60.7%)	0.002
Numbers of oocytes/embryos replaced			
GIFT	5.7 ± 2.6	6.5 ± 2.9	NS
IVF & ET	3.9 ± 2.4	4.4 ± 2.6	NS
Numbers of pregnancy per retrieval cycle	19 (21.8%)	14 (16.7%)	NS
Biochemical pregnancy[b]	4	6	
Clinical pregnancy[c]	14	7	
Ectopic pregnancy	1	1	
Numbers of abortion[d]	6 (31.6%)	14 (100%)	0.001
Biochemical pregnancy	4	6	
Clinical pregnancy	1	7	
Ectopic pregnancy	1	1	
Ovarian hyperstimulation syndrome[d]	0	5	0.0269
Mild	0	1	
Severe	0	4	

a=NS, nonsignificant
b=Biochemical pregnancy is diagnosed when the level of B-hCG > 25 mIU/ml, followed by a higher level in a subsequent assay 2 days later.
c=Clinical pregnancy is diagnosed when a gestational sac is visualized under ultrasound.
d=Fisher exact test

Serum estradiol levels on the day of hCG injection, the numbers of oocyte retrieved, numbers of oocytes/ embryos replaced and pregnancy rates were comparable in the two groups. However, there were significant differences in the requirement of hMG, the duration of GnRH-a/hMG treatment, fertilization and abortion rates, and in the incidence of ovarian hyperstimulation syndrome (Table 3).

Discussion

Various approaches for the clinical use of GnRH-a as adjuvant to control ovarian stimulation have been described. The main parameter subjected to variation is the duration of analogue administration before starting the stimulation with hMG[3, 6-10]. In the long protocol, GnRH-a is first administered for at least 10 days to induce a state of temporary hypogonadotropic hypogonadism. This is then followed by hMG administration when full ovarian suppression is achieved. In contrast, the short protocol makes use of the initial stimulatory phase of GnRH-a to augment ovarian response to hMG, which is started 2-3 days after the analogue[3,6,7,10]. This may

explain the findings in our study that a lower amount of hMG is required in the short protocol than in the long one. In this regard, short protocol may be more advantageous in term of expense. Moreover, the short protocol may be better tolerated as it involves a significantly shorter mean duration of treatment (11.3 vs 19.8 days in this study).

As can be seen in Table 1, cycle cancellation rates due to insufficient ovarian response seems to be slightly higher in the long protocol than in the short protocol. However, overall cancellation rates are not statistically different among the two protocols. It is also noticeable that cancellation due to falling E2 levels before hCG administration, which presumably signifies premature luteinization, occured in only 2 out of 186 cycles (1.1%).

Although our data show that fertilization rate is significantly higher in the long protocol than in the short one, the pregnancy rates are comparable. According to Loumaye et al[14], the "flare-up" effect in short protocol exposes the ovaries to a relatively high level of LH during the first half of the follicular phase. In their study, pregnancy rates are similar but oocyte fertilization rate and embryo quality are reduced in the short when compared with the long protocol. They postulated that high LH level in the early follicular phase may have deleterious consequences upon oogenesis. Mettler et al[15] and Dirnfeld et al[16] reported better follicular maturation and a higher pregnancy rate using the long compared with the short protocol. On the contrary, Lippitz et al[17], Zorn et al[18], Frydman et al[19] and Acharya et al[20] cannot demonstrate any advantage of the long over the short protocol regarding folliculogenesis, oocytes recovered and pregnancy rates. Obviously, a consensus has not been reached and further evaluation by means of a large enough randomized trial is needed.

Our overall clinical abortion rate of 8/21 or 38.1% is rather high when compared with 22% for IVF and 19% for GIFT as reported by the United States IVF-ET Registry in 1990[21]. It is noticeable that abortions occur significantly more often in the long than in the short protocol (7 in 7 or 100% versus 1 in 14 or 7.1%). The reason the abortion rate is much higher in the long than of that in the short protocol is not apparent. We postulate that the suppression phenomenon with a decrease in the synthesis and storage of pituitary LH and desensitization of granulosa cells may be more prolonged and more profound in the long protocol. Therefore, the rescue of luteal function by four doses of 1500 IU hCG given every three days may be adequate in the short but not in the long protocols. Further research is needed to either confirm or refute this postulation. Indeed, in a randomized controlled study of luteal support, Yovich et al[22] concluded that combined hCG/progesterone regimen provides a better outcome than hCG or progesterone alone.

It is also possible that endogenous hCG produced by the conceptus may not be sufficient to sustain luteal function and hCG supplementation should be given well beyond the implantation period when long stimulation protocol is used. Although they present no direct evidence to support their recommendation, Brinsden and Asch[23] continued progesterone supplementation until 10 weeks' gestation if their GIFT pregnancies were normal. Our data suggest that such supplementation may be necessary in the long protocol, but its value in the short protocol should be further evaluated.

Ovarian hyperstimulation (OHSS) occurred in 5/171 stimulated cycles, giving an incidence of 2.9%. In this report, all cases of OHSS occurred in the long protocol group. This may be related to the finding that more follicles are recruited as evidenced by a higher level of E2 on the day of hCG injection and the higher mean number of oocytes retrieved. The details of this serious complication in our patients have been described previously[24].

This study has limitations in that it is a retrospective review and patient allocation is not randomized. Moreover, it is possible that significant differences in pregnancy rates among the two GnRH-a protocols exist but we do not have a large enough sample size to show the difference. However, based on our limited data short protocol may be more preferable than long protocol in terms of patients' expense and convenience. A further randomized trial is needed to evaluate the two protocols. Luteal phase support should also be a subject for future evaluation.

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